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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/259,929	03/01/1999	ANTHONY CERAMI	10162-004-99	5875

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/259,929	CERAMI ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14,17-19,48,50 and 58-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-14,17-19,48,50 and 58-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 8/14/2008. Claim(s) 7, 15-16, 20-47, 49, 51-57 have been cancelled. Claim(s) 1-6, 8-14, 17-19, 48, 50, 58-61 are pending. Claim(s) 60-61 have been amended. Claim(s) 1-6, 8-14, 17-19, 48, 50, 58-61 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejections of the last Office Action are maintained for reasons of record and modified below as a result of Applicant's amendments to the claims. The following new rejections will also apply.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6, 8, 10, 12-13, 48, 50, 60-61 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claim 76 of copending Application No. 10/783,052. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims sufficiently overlap in scope. The latter claims are directed to a method of modulating the immune response in a mammal to an antigen by implanting a device comprising a polymeric material containing the antigen within a second polymeric material, where all of the polymers overlap in scope and the forms of administration are disclosed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Examiner acknowledges Applicant's request to hold the double patenting rejection in abeyance until allowable subject matter is identified.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8-10, 12-13, 50, 58-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu (WO 93/17662, of record).

Yu teach an implant device of releasing an active ingredient in an animal following administration, wherein the implant device comprises a membrane forming a

wall around a core matrix containing the active ingredient (abstract). The device may be adapted readily adapted for immediate continuous release or immediate or delayed pulsatile release. The bioactive molecules in the active ingredient comprise any native, synthetic, or recombinant pharmaceutical agent including antigens, antibodies, and immune stimulants or suppressants (pg. 3, lines 3-4, 24-26). The majority of the active material will be delivered or released through a pre-determined region in the wall encasing the body member. The pre-determined region may be a pore, outlet, exit, channel, or other passage formed within the body wall or may be a region defined during manufacture which is not covered by the wall (pg. 5, lines 5-10). Tiny holes can be made through the end coating so as to provide even slower and longer lasting release of the active material (pg. 15, lines 18-22). Multiple layers of matrix (pg. 8, lines 10-12) may consist of polymers including polylactic acid/polyglycolic acid copolymer and n-butyl cyanoacrylate copolymer (pg. 9, lines 19-26) as well as gelatin agar matrix (pg. 10, line 12) and collagen poly(HEMA) hydrogel (col. 16, line 8).

Claims 1-4, 6, 8-10, 12-13, 50, 58-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Emery et al. (US Patent 5,538,733, of record).

Emery et al. teach a method of priming an immune response in an animal by administering a biocompatible and non-toxic solid phase implant containing an immunogenic agent (abstract). The implant may be formed from polylactide, polyglycolide, or other like polymers or copolymers thereof (col. 2, lines 39-48) as well as polyethylene, ethylene-vinyl acetate copolymer, polyvinyl pyrrolidone, polyvinyl

alcohol, among others (col. 5, lines 1-18). The immunogenic agent may be any antigenic substance that is capable of stimulating an immune response in the animal being treated (col. 5, lines 33-35). The matrix may be formulated to include a soluble or insoluble pore-forming agent, for example polymers, that will dissipate from the matrix causing the formation of pores and/or channels throughout the implant matrix (col. 9, lines 29-40). The in vivo release rate and extent or release of the immunogenic agent from the solid implant matrix over a period of 1-90 days may be effectively controlled and optimized by varying the matrix formulation as well as varying the type, amount, size, shape, and porosity of the matrix according to practices known and used in the art (col. 10, lines 15-46). The amount of immunogen released from the implant will effectively induce a primary immune response in the animal, so that the animal will respond by the production of antibodies (col. 10, lines 51-55).

Claims 1-4, 6, 8-10, 12-13, 50, 58-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Barr et al. (US Patent 5,593,697, of record).

Barr et al. teach a pharmaceutical implant comprising a water insoluble material containing an antigen within a polymer coat (abstract) for the prophylactic or therapeutic vaccination (col. 3, lines 16-21) of a mammal (col. 4, lines 32-36). Vaccines against bacterial, viral, fungal, or protozoal infections of animals or humans may be utilized in the device of this invention (col. 6, lines 61-64). Barr et al. disclose that those skilled in the art will be able to recognize the various biocompatible polymers that can be used in this invention (col. 3, lines 52-55). One or more layers of different polymers may be

used and when exposed to normal physiological pH conditions, the rupture time of the antigen from the polymer coat is typically between 14 to 45 days (col. 4, lines 9-14). This bilayer film coating forms an impermeable barrier to the antigen until such time for rupture (col. 5, lines 1-16). The preferred polymers are but not limited to polyethylene, silicone, acrylic resins, and polylactide-glycolide copolymers (col. 5, line 60 to col. 6, line 15). Barr et al. discloses that those skilled in the art will also appreciate that other biodegradable polymers may be used in this device. The thickness and permeability of the films can be varied by the type of polymer and/or the addition of more than one polymer so as to form a delayed release formulation. The film formed from Eudragit NE30D forms an insoluble outer coat over the film designated S. This outer film controls the access of physiological fluid to the inner S film (col. 5, lines 46-57). Ethyl cellulose is an insoluble polymer, thus when the PLGA polymer in the EC/PLGA film hydrolyses the film become porous, allowing release of the payload. Bar et al. teaches the disadvantages of using pure PLGA copolymers, which is difficult to film coat onto implant cores using conventional film coat equipment, as the film becomes tacky causing the cores to aggregate and then separate which leads to picking (holes in the film). Therefore, a blend of EC/PLGA, which has a higher Tg, is used, thus remedying this problem (col. 6, lines 13-36). Finally, Barr et al. disclose that the invention is susceptible to variations and modifications other than those specifically described (col. 15, lines 20-23).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5, 11, 14, 17-19, 48, 60-61 are rejected under 35 U.S.C. 103(a) as being obvious over Yu, Emery, or Barr et al. as applied to claims 1-4, 6, 8-10, 12-13, 50, 58-59 in view of Andrianov et al. (US Patent 5,529,777, of record).

The instant claims are directed to a method of modulating the immune response in a mammal to an antigen by implanting a device comprising a polymeric material containing the antigen within a second polymeric material.

Yu, Emery, and Barr et al. teach as disclosed above, however, fail to specifically disclose delayed and multiple antigen introduction to device, subsequent removal of device, preparation of hybridoma for the production of a monoclonal antibody, and perforations approximately 1/16 to 1/32 of an inch in diameter and 10 perforations per centimeter.

Examiner notes that since Yu, Emery, and Barr et al. incorporate pores in the implant device, it is obvious for one of ordinary skill in the art to optimize the size and number of perforations to 1/16 to 1/32 of an inch in diameter and 10 perforations per centimeter because of the reasonable expectancy to successfully release the active agent in the desired concentration and rate. Furthermore, the cited prior art references teach that the invention is susceptible to variations and modifications other than those specifically described. Therefore, it is obvious to optimize the invention so that the antigen can be repeatedly introduced to the device, for example 2-4 days after implantation.

"When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382 "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." MPEP 2114.04.

Andrianov et al. teach antigens encapsulated by polymers to form microparticles to induce an immune response in an animal (col. 25, lines 50-57). The preferred biodegradable polymers include polycarbonates, polyesters, polyurethanes, polyamides, polyvinyl alcohol (PVA), gelatin, alginate, polyvinylpyrrolidone (PVP), methyl cellulose (col. 4, lines 1-37), polystyrene, polyvinyl acetate, and copolymers of the polymers or monomers thereof (col. 5, lines 9-21). Andrianov et al. also disclose

encapsulating hybridoma cells in the microspheres (example 1). Andrianov et al. also disclose the production of antibodies by oral administration of an influenza vaccine in a polymer to mice as measured by in vitro and in vivo immune response studies (example 4). In the same manner, Example 7 and Table 6 also show harvesting of immune cells (IgC isotopes of the antibodies) in the parental immunization of mice with influenza particles formulated in polymeric microspheres. In this manner, it has been shown that the device containing the immune cells have been removed from the body before the apparent rupture period to begin the harvesting procedure.

It is noted that hydroxylated polyvinyl acetate is obvious over the teaching of polyvinyl acetate since a genus render the species obvious. Examiner notes that this is a typical genus/species situation. Once a *prima facie* case of obviousness is established, the burden is shifted to the Applicant for objective evidence for nonobviousness. See MPEP 2144.08.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have removed the device after 10 days to begin harvesting of immune cells for the preparation of a hybridoma as taught by Andrianov et al.

A person of ordinary skill in the art would have been motivated to have removed the implant device after 10 days from the body to begin harvesting of immune cells for the preparation of a hybridoma because: (1) Yu, Emery, and Barr et al. as well as Andrianov et al. teach implant devices comprising antigens encapsulated by polymers to induce an immune response in an animal; and (2) the added advantage of forming a

hybridoma for the production of a large amount of a specific antibody. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in removing an implant device after 10 days from the body to harvest immune cells for the formation of hybridoma cells for the production of an antibody in modulating an immune response in a mammal.

Response to Arguments

Applicant argue that neither Barr nor Andrianov discuss perforations in the device at the time of implantation or perforation of the number or diameter disclosed by the claimed invention. Specifically, Barr's outer layer, called "film coating," does not feature any perforations and, as a result, is completely impermeable prior to rupture. Applicant cites col. 6, lines 28-32 to explain why Barr uses a film coat comprised of EC/PLGA copolymer as opposed to merely using PLGA, since the film becomes tacky causing the cores to aggregate and separate which leads to picking (holes forming in the film). It is evident that Barr does not consider this being desirable given that it goes on to state that a blend of EC and PLGA has a higher glass transition temperature and therefore leads to a higher quality film. Furthermore, the presence of perforations would frustrate the purpose of the Barr invention by facilitating the flow of physiological fluid inside Barr's device resulting in immediate release of the antigen, rather than the desired delayed release.

This is not persuasive because Applicant has clearly misread the Barr reference. The use of 100% PLGA film coat, results in unwanted aggregation and separation of the

cores, which then leads to picking (holes forming in the film). Because such aggregation and separation of the cores is not desired, Barr uses a blend of EC and PLGA polymers, which has a higher glass transition temperature and therefore leads to a higher quality film. This issue with using a blend or not has nothing to do with whether Barr intended for the film coat to have holes. Nonetheless, it is clear that Applicant's interpretation of Barr is incorrect since it is taught that the outer film coat controls access of physiological fluid to the core matrix (col. 5, lines 44-49). Moreover, it is taught that release of the payload goes through pores in the film after it becomes hydrolyzed (col. 6, lines 19-21 and 41-43). The time at which pores start to form depends on the weight percent of the film and the percentage of ethyl cellulose.

Applicant argues that since Barr teaches rupture of the device and release of the antigens into the body, there would be no motivation for removing the devices in hopes of harvesting immune cells given their recognition that the immune cells would converge on the antigens released from the device. Further, Barr does not disclose the presence of immune cells within the Barr device because the immune response would be ongoing in the tissues surrounding the device.

This is not persuasive because the obviousness rejection is based on removing the device prior to rupture of the device and subsequent release of the antigens. Specifically, Barr teaches the rupture period to be from 14 to 45 days, therefore removal of the implant device from the body even after 10 days would be before any material of interest becomes available to the tissues surrounding the device. Andrianov et al.

teaches removal of the device containing immune cells before the apparent rupture period to being harvesting the immune cells for production of antibodies.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Cerami Hand Declaration under 37 CFR 1.132 filed 8/14/2008 is insufficient to overcome the rejection of claims 5, 11, 14, 17-19, 48, 60-61 under 35 U.S.C. 103(a) as being obvious over Yu, Emery, or Barr et al. as applied to claims 1-4, 6, 8-10, 12-13, 50, 58-59 in view of Andrianov et al. (US Patent 5,529,777, of record) as set forth in this Office action.

This is not persuasive because a Declaration cannot overcome an anticipatory rejection or an obviousness rejection where the independent claims were rejected in an anticipatory rejection. Nonetheless, the Cerami Hand Declaration does not show unexpected results, but only evidence that the claimed invention is enabled or works as intended. It is not commensurate with the scope of the claims, since all antigens and polymeric material are recited in claim 1. Furthermore, there is no side-by-side comparison with the closest prior art. Applicant is reminded that implant devices containing antigens that modulate an immune response are well known in the art.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax

phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S Chong/
Examiner, Art Unit 1617

YSC